<Date of submission>

Submission of comments on '<Reflection paper on establishing efficacy based on single arm trials submitted as pivotal evidence in a marketing authorisation : Considerations on evidence from single-arm trials >' (EMA/CHMP/564424/2021)

https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-establishing-efficacy-based-single-arm-trials-submitted-pivotal-evidence-marketing_en.pdf

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EMA/CHMP/564424/2021

Comments from:

Name of organisation or individual
Prescrire

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	This document rightly highlights the methodological weaknesses of non-comparative trials as a tool for evaluating the potential efficacy of a medicinal product. It is because of these weaknesses that, with a few rare exceptions, marketing authorisations should not be based on such trials. Non-comparative trials can only support hypotheses, which should then be tested in double-blind randomised comparative trials (1). Patients and healthcare professionals need a causal relationship to have been established between a treatment and a clinical improvement of sufficient value that it justifies exposure to the treatment's known, and as yet unknown, harms (1). It is highly regrettable that this document fails to spell out clearly what non-comparative trials can generally provide (support for hypotheses) and what they cannot (the design does not allow a causal relationship to be inferred between observed outcomes and the treatment administered). It is regrettable that EMA does not define very clearly in this document, from the outset, the few exceptional situations in which a non-comparative trial might be considered an acceptable basis for marketing authorisation. These situations must be precisely defined to prevent the unjustified use of non-comparative trials, to the detriment of the quality of	

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	drug evaluation and, ultimately, the quality of patient care. And even in these unusual situations, the endpoints should be clinical outcomes, or validated surrogate outcome measures for which a correlation has been demonstrated between short-term changes in this measure and long-term clinical outcomes (such as viral load in the evaluation of antiretroviral drugs), and not simply unvalidated surrogate endpoints. Despite the weaknesses of non-comparative trials, we have noticed that EMA has been accepting them increasingly as the sole basis for marketing authorisations, in an evaluation based primarily on surrogate rather than clinical endpoints. Examples include idecabtagene vicleucel in multiple myeloma, tafasitamab in diffuse large B-cell lymphoma, selumetinib for plexiform neurofibromas, sotorasib in non-small cell lung cancer with a KRAS G12C mutation, and tisagenlecleucel in refractory or relapsed follicular lymphoma (2-6). Even with a clinical endpoint, the use of a non-comparative trial as a basis for marketing authorisation must remain the exception. Randomised comparative trials are feasible in most situations, even in rare diseases. Nusinersen, for example, was evaluated in spinal muscular atrophy in a comparative trial (7). Patients with rare diseases are entitled to high-quality	

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	clinical evaluations, like any other patient. To require high-quality evaluations means to be on the side of today's patients, and even more so of tomorrow's patients.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
140-146		Comment: Because of their design, non-comparative clinical trials are unable to demonstrate a direct causal link between a treatment and an observed outcome. The value of such trials is in providing support for hypotheses, which must subsequently be tested in randomised comparative clinical trials. Proposed change (if any): *Isolation of treatment effect* There is no general statistical or methodological definition for the concept of isolating a treatment effect~~. For the purpose of this reflection paper, the following definition is adopted. If observed individual outcomes in a SAT for the defined endpoint within the designated follow-up could not have occurred without active treatment in any patient who entered the trial, the SAT is able to isolate the treatment effect on that specific endpoint. Conceptually, this can allow a causal interpretation of the effect of the treatment, despite the limitations in study design~~ ***Because of their design, non-comparative clinical trials are unable to demonstrate a direct causal link between treatment and the observed outcome. The aim of these trials is to underpin hypotheses that need to be tested afterwards in randomised controlled trials.***	
157-159		Comment: "the primary objective of the SAT may be the isolation of a treatment effect on an endpoint or the estimation of the size of the treatment effect". Here again, these non-comparative trials can only provide support for	

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		hypotheses: they demonstrate nothing. Proposed change (if any): Depending on the therapeutic area and the development programme, the primary objective of the SAT ***is to suggest*** ~~may be the isolation of~~ a treatment effect on an endpoint or the estimation of the size of the treatment effect.	
172-176		Comment: The internal validity of a non-comparative trial is irretrievably lower than that of a randomised comparative trial. Whatever methodological measures are taken to reduce bias, a non-comparative trial will never provide evidence of equivalent quality to that provided by a comparative trial, because it cannot demonstrate causation. Proposed change (if any): Internal validity ***Because of their design***, the internal validity of a SAT (compared to a well-designed RCT) can***not*** be conceptualised as the systematic difference between the treatment effect estimate from the SAT and the treatment effect estimate that would have resulted from the matching RCT ***even if it had*** ~~had it~~ been conducted in the same population and had the test treatment thereby been calibrated against a (placebo) control arm. ~~**This matching RCT can be understood as the target trial for the SAT.**~~ The absence of the randomised control arm ~~**substantially increases the risk**	

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		~~**of bias and thus**~~ ***irretrievably*** reduces internal validity.	
203		Comment: Well-designed double-blind randomised trials (featuring, in particular, clinical endpoints, a statistical analysis plan, and inclusion and exclusion criteria) are the most suitable method for evaluating efficacy: "in general" has no place in this statement. Proposed change (if any): ~~**In general,**~~ RCTs are the most suitable method to provide reliable estimates of clinical efficacy.	
209-211		Comment: The primary endpoint must always be the most clinically relevant endpoint from the patients' perspective. Proposed change (if any): ~~**In general,**~~ The primary efficacy endpoint for the main trial(s) aiming to establish efficacy should ***always*** reflect the variable capable of providing the most clinically relevant ***patient-oriented*** evidence ~~**directly related to the primary objective of the trial**~~	
213-216		Comment: The primary endpoint must be able to demonstrate the CLINICAL efficacy of the treatment; surrogate endpoints must be avoided. Proposed change (if any): For a SAT the primary endpoint	

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		must also be able to isolate ***clinical*** treatment effects (see Section 3), i.e. it is required that the primary endpoint is such that it is known that observations of the desired ***clinical*** outcome would occur only to a negligible extent (in number of patients or size of the effect) in the absence of an active treatment	
231		Comment: A novel mechanism of action should not, in and of itself, determine how a drug is evaluated. A novel mechanism of action simply suggests that the drug might be effective. Proposed change (if any): The acceptability of a SAT and its primary endpoint strongly depend on the clinical context ~~**and mechanism of action of the drug**~~ and are therefore a case-by-case and disease area specific decision.	
34-39		Comment: Despite all the scientific advice EMA has provided for pharmaceutical companies, experience shows that it has not always improved the quality of trials, due in particular to the non-binding nature of this advice (8,9). The advice EMA provides to companies puts the Agency in the role of a contributor to and the assessor of their marketing authorisation applications, lessening its impartiality. Proposed change (if any): ***If an applicant plans to base a marketing authorisation on a SAT***, It is ***his*** ~~**the**~~	

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		responsibility ~~of the applicant~~ to adequately justify to regulators why a SAT, which deviates from the standard approach of providing pivotal evidence on efficacy through RCTs, can provide clear pivotal evidence of efficacy. ~~**Obtaining scientific advice is therefore strongly recommended to discuss whether pivotal evidence from SATs may be considered acceptable for seeking marketing authorisation for a specific development programme**~~**.**	
203-205		Comment: Despite all the scientific advice EMA has provided for pharmaceutical companies, experience shows that it has not always improved the quality of trials, due in particular to the non-binding nature of this advice (8,9). The advice EMA provides to companies puts the Agency in the role of a contributor to and the assessor of their marketing authorisation applications, lessening its impartiality. Proposed change (if any): ~~**In general,**~~ RCTs are the most suitable method to provide reliable estimates of clinical efficacy. ~~**However, in certain situations, evidence from SATs may be considered acceptable for marketing authorisation, and in such cases obtaining scientific advice is recommended.**~~ ***It is the responsibility of the applicant to adequately justify to regulators why a SAT is adequate in this situation given that it deviates from the standard approach of providing pivotal evidence on***	

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		efficacy through RCTs.	
336-344		Comment: Despite all the scientific advice EMA has provided for pharmaceutical companies, experience shows that it has not improved the quality of trials, due in particular to the non-binding nature of this advice (8,9). One very good example is the evaluation of risperidone as monthly injections (Okedi°). EMA's advice stipulated that the company "*should follow the CHMP guideline for medicinal products including depot preparations in the treatment of schizophrenia (EMA/CHMP/40072/2010 Rev. 1) and the different proposals of clinical development programme including comparator arm such as risperidone*". The company did not follow this advice and used only placebo as the comparator in its trial in patients with acutely decompensated schizophrenia, disregarding the most basic ethics concerning the treatment of trial participants, set out in the Declaration of Helsinki (9,10). Proposed change (if any): Due to the lack of a comparator within the trial, the role of relevant external (extra-study) information is critical for the interpretation of the results derived from a SAT. External information may take the form of (i) general knowledge about the natural course of the disease, e.g. that an endpoint will not change without active treatment, or (ii) external clinical data. Use of external information in the analysis or interpretation of a SAT is a	

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		crucial design element and should be pre-specified in the study protocol. Most importantly, any external information used to describe the hypothetical control condition (counterfactual) of the SAT should include a precise and a priori definition and description of the control condition(s) to be covered. ~~**It is strongly recommended to seek scientific advice on the use and the choice of external information before the study protocol of the SAT is finalised**~~	
351-357		Comment: In the very rare cases in which a non-comparative trial is acceptable for evaluating a medicinal product's efficacy, because the clinical course of the disease is generally catastrophic in the short term, an indirect comparison is necessary, despite the multiple forms of bias inherent in indirect comparisons. Proposed change (if any): ~~**In exceptional cases**~~, ***In the exceptional cases where a SAT is acceptable to assess a drug's efficacy***, ~~**the assessment of efficacy is envisaged to be informed by a**~~ ***an in***direct comparison ~~against~~ **versus** external clinical data (i.e. an external control) ***is to be considered***. Guidance on the choice of and comparison with external data is beyond the scope of this reflection paper. While methods that directly incorporate external data into the analysis come with a promise to provide useful insights and potentially	

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		reduce bias, they add complexity to pre-specification and rely on additional assumptions that are often not transparent. Consequently, approaches that directly incorporate external data should be carefully evaluated on a case-by-case basis.	

References

1- Prescrire Editorial Staff "Proving a treatment's efficacy. Double-blind randomised comparative trials, the foundations of a rigorous scientific approach" *Prescrire Int* 2023; **32** (249): 162-165.

2- Prescrire Editorial Staff "Idecabtagene vicleucel (Abecma°) in multiple myeloma after failure de several lines of treatment" *Prescrire Int* 2022; **31** (243): 294.

3- Prescrire Editorial Staff "Tafasitamab (Minjuvi°) in relapsed or refractory diffuse large B-cell lymphoma" *Prescrire Int* 2023; **32** (248): 128.

4- Prescrire Editorial Staff "Selumetinib (Koselugo°) in plexiform neurofibromas due to neurofibromatosis type 1" *Prescrire Int* 2023; **32** (248): 120-122.

5- Prescrire Editorial Staff "Sotorasib (Lumykras°) in non-small cell lung cancer with KRAS G12C mutation" *Prescrire Int* 2023; **32** (248): 123-124.

6- Prescrire Editorial Staff "Tisagenlecleucel (Kymriah°) in refractory or relapsed follicular lymphoma" *Prescrire Int* 2023; **32** (249): 153.

7- Prescrire Editorial Staff "Nusinersen (Spinraza°) in spinal muscular atrophy: insufficient data" *Prescrire Int* 2018;**27** (199): 290.

8- Prescrire Rédaction ""Conseils scientifiques" de l'EMA aux firmes: menace pour l'indépendance" *Rev Prescrire* 2015; **35** (384): 780-781.

9- Prescrire Rédaction "Rispéridone en injections mensuelles (Okedi°)" *Rev Prescrire* 2023; **43** (475): 336-337.

10- EMA CHMP "Public assessment report for Okedi. EMEA/H/C/005406/0000" 16 December 2021: 100 pages.